Lactic acid: Summary Report

Summary Report

Lactic acid

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Frequently Used Abbreviations

AHA	Alpha-hydroxy acid
API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of lactic acid (UNII code: 33X04XA5AT), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how lactic acid is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how lactic acid has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of lactic acid and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Lactic acid was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA) and Sincerus Florida LLC. Lactic acid was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Lactic acid was nominated to treat unknown medical conditions, although according to the nominator, it generally is used to treat seborrheic dermatitis, warts, and periorbital melanosis via various topical dosage forms, including gel, cream, solution, shampoo, etc., in strengths based on prescriber's request (5-30%, 88%).

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of lactic acid.[6-8]

Reasons provided for nomination to the 503B Bulks List included:

- Compounded product may be the only product to effectively treat the indication for which it is intended
- Patient need for dosage form or strength, including greater concentration, that is not available commercially
- Patient sensitivities to dyes, fillers, preservatives or other excipients in manufactured products
- Individual finished products have a considerable variance in the actual amount of active product ingredient and the use of a finished product has the potential to introduce unacceptable inaccuracies into the compounded medication
- The requesting physicians have determined that there is a clinical difference between the compounded drug being requested and the commercially available one

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of lactic acid products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for lactic acid; name variations of lactic acid were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing lactic acid. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: lactic acid, topical administration, and substances nominated for use in combination with (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on April 13, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on April 13, 2020 for clinical practice guidelines that recommended the use of lactic acid and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which lactic acid was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language

other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if lactic acid was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which lactic acid was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of lactic acid; setting; total number of patients; number of patients who received lactic acid; patient population; indication for use of lactic acid; dosage form and strength; dose; ROA; frequency and duration of therapy; use of lactic acid in a combination product; use and formulation of lactic acid in a compounded product; use of lactic acid compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances lactic acid was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify the following medical specialties that would potentially use lactic acid: dermatology. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of lactic acid in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the

identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1, were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Lactic acid is not available as an FDA-approved product in the nominated dosage form and ROA.
- Lactic acid is available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for lactic acid.
- Lactic acid is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Ireland, Namibia, Saudi Arabia, and the UK.

Table 1. Currently approved products – US

No approved products in the US

Table 2. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Lactic acid, lactoserum atomizate, phosphoric acid	–	Solution	Topical	Abu Dhabi	Active	–
Lactic acid, polidocanol, salicylic acid	0.5 g/10 g	Solution	Topical	Abu Dhabi	Active	–
Lactic acid, podophyllum resin, salicylic acid	137.5 mg/mL	Paint	Topical	Australia	S2 – Pharmacy medicine	09/30/1991
Lactic acid, lactoserum atomisat	0.07 g/100 mL	Solution	Topical	Abu Dhabi	Active	–

Lactic acid, salicylic acid	4-16.7%	Gel, lotion, paint, solution	Topical	Abu Dhabi	Active	–
				Australia	S2 – Pharmacy medicine	09/12/1991
				Ireland	Pharmacy-only	01/21/1977
				Namibia	–	08/20/2008
				Saudi Arabia	Prescription	–
				UK	Pharmacy	02/14/1990
Lactic acid, sodium hyaluronate	1 g/100 g	Solution	Oral, topical	Abu Dhabi	Active	–
Lactic acid, urea	55.5 mg/g	Cream	Topical	Abu Dhabi	Active	–

Abbreviation: "– ", not mentioned.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Results of literature review

Study selection

Database searches yielded 786 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 646 titles and abstracts were screened. After screening, the full text of 263 articles was reviewed. Finally, 39 studies were included. Two hundred twenty-four studies were excluded for the following reasons: wrong study design (195 studies); lactic acid used as brand or proprietary product (16); wrong substance (7); duplicate study (3); language other than English (2); lactic acid only mentioned briefly (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 39 included studies were published between 1976 and 2020. There were 25 experimental studies, 4 observational studies, 6 descriptive studies, and 4 clinical practice guidelines. The 39 studies were conducted in the following countries: Egypt, Germany, India, Iran, Korea, Lebanon, Pakistan, Sudan, Sweden, Thailand, UK, and US.

A total of 1558 patients participated in the 39 included studies. The number of patients in each study ranged from 1 to 210.

Outcome measures differed among the included studies and included: reduction or cure of skin condition, time to cure, adverse reactions, safety and efficacy.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of lactic acid

Five hundred sixty-four patients received lactic acid as an experimental treatment for warts, administered topically in strengths ranging from 15-17%. Duration of treatment ranged from 3 weeks to 3 months. Two hundred thirty-seven patients received lactic acid as an experimental treatment for melasma, administered topically in strengths ranging from 14-92%. Duration of treatment ranged from 6 to 20 weeks. One hundred eight patients received lactic acid as an experimental treatment for acne, administered topically in strengths of 10.4-14%. Duration of treatment ranged from twice to 12 weeks. Twenty-one patients received lactic acid as an experimental treatment for ichthyoses, administered topically in doses ranging from 5-10%. Duration of treatment ranged from 4 weeks to indefinite. Seventy-five patients received lactic acid as an experimental treatment for photodamage, administered topically in strengths ranging from 6.5-7.8%. Duration of treatment ranged from once to 16 weeks. Thirty patients received lactic acid as an experimental treatment for actinic keratoses, administered once topically in a strength of 14%. Twelve patients received lactic acid as a treatment for aging neck skin, administered once topically at a 14% strength. Sixty patients received lactic acid as an experimental treatment for atrophic acne scarring, administered topically at 85% strength for 6 to 18 weeks. One hundred thirty-two patients received lactic acid as an experimental treatment for chemical peels in skin types III-VI, administered at least once topically at 88% strength. Eight patients received lactic acid as a treatment for facial hyperpigmentation, administered once topically. Nine patients received lactic acid as a treatment for frictional asymptomatic darkening of extensor surfaces, administered topically at 12% strength. Duration of treatment ranged from 1 month to 3

years. One patient received lactic acid as a treatment for infection caused by gram-negative bacilli, administered topically at 10% strength. Fifty patients received lactic acid as an experimental treatment for keratosis pilaris, administered topically for 12 weeks at 10% strength. One patient received lactic acid as a treatment for lichen planus pigmentosus, administered topically for 16 weeks. One hundred one patients received lactic acid as an experimental treatment for molluscum contagiosum, administered topically until lesions cleared or a maximum of 30 days at 16.7% strength. One hundred thirty-seven patients received lactic acid as an experimental treatment for palmar-plantar erythrodysesthesia, administered topically for 3 weeks at 6% strength. Twelve patients received lactic acid as a treatment for xerosis of the foot, administered topically for 4 weeks.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Lactic acid was used as a compounded product and was used in a combination product (refer to Tables 8 and 9).

In 20 studies, the authors' concluding statement recommended the use of lactic acid for the treatment of acne, actinic keratoses, aging neck skin, atrophic acne scarring, facial hyperpigmentation, ichythyoses, infection caused by gram-negative bacilli, lichen planus pigmentosus, melasma, photodamage, warts, and xerosis of the foot.[9-28] In 7 studies, the authors concluded that the use of lactic acid was not recommended for the treatment of acne, palmar-plantar erythrodysesthesia, photodamage, and warts.[29-35] In 2 studies, the authors' concluding statement did not support a significant difference in effectiveness between lactic acid and salicylic acid for melasma or keratosis pilaris.[36,37] In 1 study, the authors' concluding statement was that both glycolic acid 70% and Jessner's solution, which contains lactic acid in combination with other APIs, worked equally well for the treatment of melasma when combined with tretinoin and hydroquinone.[38] In 1 study, the authors concluded that while Jessner's solution displayed an early additive effect to laser treatment, this effect was not consistent after four sessions.[39] In 1 study, the authors concluded that both pyruvic acid and compounded salicylic acid / lactic acid solutions were effective and similar in decreasing the number, size, and recurrence of warts.[40] In 1 study, the authors' concluding statement was that superficial chemical peels have a relatively low complication rate in standardized administration on darker skin types.[41] In 1 study, the authors concluded that there was no statistical difference between Jessner's peel followed by trichloroacetic acid when compared to fluorouracil cream for the treatment of facial actinic keratoses.[42] In 1 study, the authors' concluding statement was that both potassium hydroxide and salicylic acid / lactic acid were effective for the treatment of molluscum contagiosum, with neither intervention showing superiority; however, the salicylic acid / lactic acid treatment showed fewer side effects.[43] In 1 study, the authors' concluding statement was that in most scenarios, treatment with either lactic acid or urea cream is at least partially effective for the treatment of frictional asymptomatic darkening of extensor surfaces.[44] Clinical practice guideline from the Indian Association of Dermatologists did not provide a conclusion on the use of lactic acid for the treatment of active acne and epidermal melasma other than that peels of superficial or medium depth are safer for Indian patients.[45] Clinical practice guidelines for psoriasis from the American Academy of Dermatology did not recommend the use of topical agents as monotherapy in extensive disease, or disease that is limited, but recalcitrant.[46] Clinical practice guidelines for cutaneous warts from the British Association of Dermatologists stated that the most commonly used OTC products are salicylic acid paints, which are often mixed with lactic acid.[47]

Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

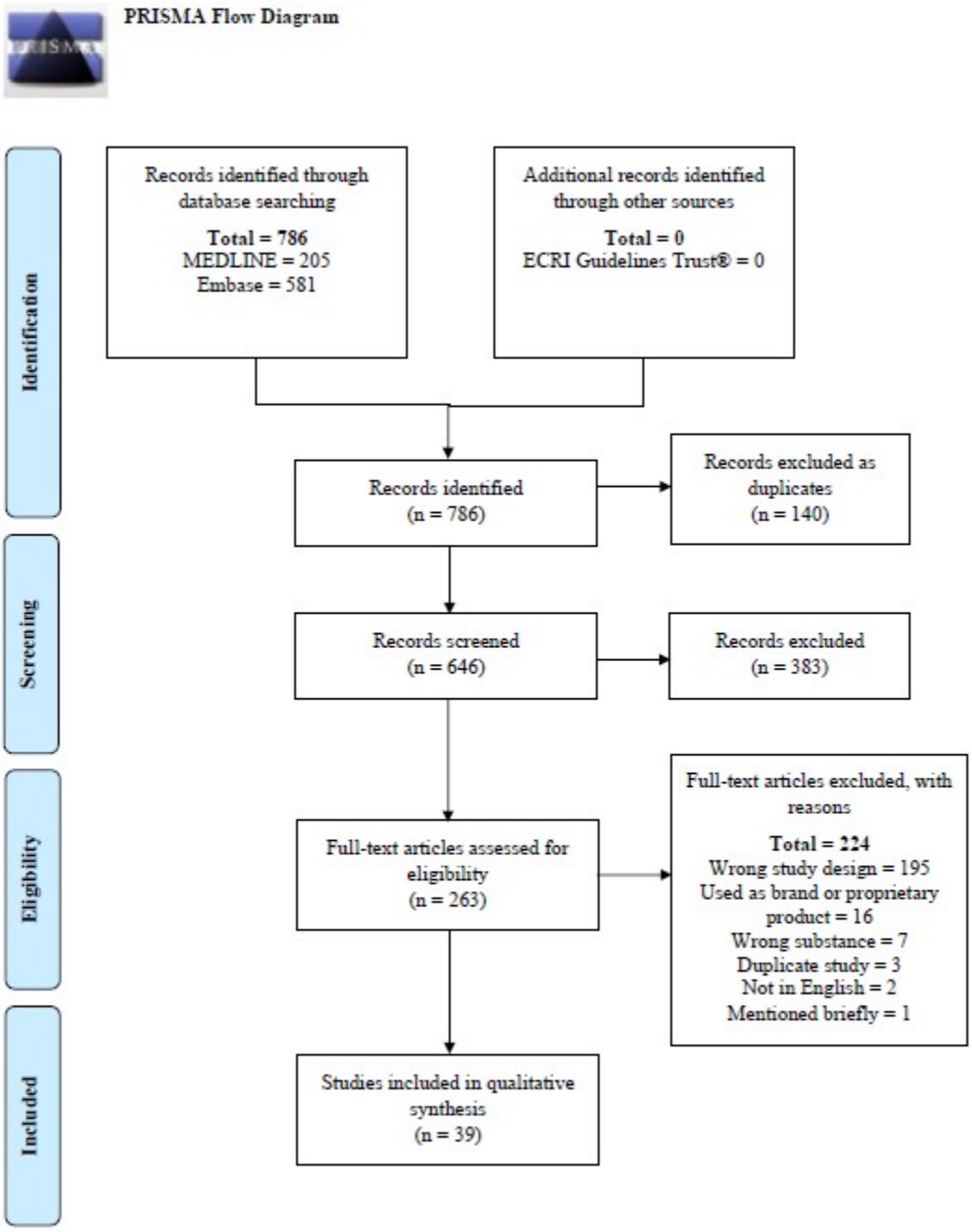
In addition to the 39 included studies, 2 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of lactic acid.

Lactic acid is part of a drug class known as alpha-hydroxy acids (AHAs) that include other products such as glycolic acid, malic acid, citric acid, alpha-hydroxyethanoic acid, alpha-hydroxyoctanoic acid, alpha-hydroxycaprylic acid, hydroxycaprylic acid, and hydroxyl fruit acids.[48] Of these acids, the two most commonly used in cosmetics are glycolic acid and lactic acid.[48] The concentration of AHAs in OTC products must be less than 10%, though mild peels ranging from 10-40% can be used in salons by trained professionals.[48] If peels have a concentration greater than 40%, they can only be used by medical doctors.[48] AHAs speed up the normal process of skin regeneration and exfoliation by reducing the dead layer of surface skin cells (corneocytes), and at higher concentrations (25%) they "can cause increased epidermal or papillary dermis thickness, increased acid mucopolysaccharides, improved quality of elastic fibers, and increased collagen density. They also can promote increased gene expression of collagen and hyaluronic acid in the dermis and epidermis."[48] The degree of exfoliation is directly related to how long the product is applied and higher concentrations are associated with increased effects in anti-aging.[48]

Jessner's solution, which is composed of resorcinol (14 g), salicylic acid (14 g), and 85% lactic acid (14 mL) and 95% ethanol quantum satis 100 mL, has been used for over 100 years as a peeling agent and treatment for epidermal lesions.[29,30] Each component has a specific purpose: resorcinol disrupts keratin bonds; salicylic acid removes intercellular lipids that "are covalently linked to the cornified envelope surrounding epithelial cells;" and lactic acid causes corneocyte detachment and stratum corneum desquamation.[30]

According to a recent algorithm, the main indications for chemical peeling are pigmentary disorders (lentigines, ephelides, and melasma); inflammatory disorders (acne and rosacea); scarring (acne scarring, traumatic scarring, and surgical scarring); chronoaging (superficial and medium-depth rhytides); and precancerous lesions (actinic keratoses).[49] According to this algorithm, lactic acid peels fall under the category of "superficial peels," where the goal is to treat dermatologic conditions that are just in the epidermis and to minimize recovery time and side effects.[49] Jessner's solution is used as a potential pretreatment primer to disrupt the cornified layer before medium-depth peels of glycolic acid (medium to high concentration) and trichloroacetic acid (low to medium concentration).[49]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	Number of Studies
Descriptive[13,18,20,23,27,44]	6
Experimental[9-12,14-16,19,21,22,24,26,29-36,38-40,43,50]	25
Observational[17,28,41,42]	4
Guidelines[25,45-47]	4

Table 4. Number of studies by country

Country	Number of Studies
Egypt[9-11]	3
Germany[25]	1
India[15,30,31,45]	4
Iran[40]	1
Korea[29,32,39]	3
Lebanon[33]	1
Pakistan[24,36]	2
Sudan[43]	1
Sweden[19]	1
Thailand[50]	1
UK[26,47]	2
US[12-14,16-18,20-23,27,28,34,35,38,41,42,44,46]	19
	Total US: 19 Total Non-US Countries: 20

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Warts					
Deshmukh *et al.*, 2020, India[31]	Prospective study	60 Patients with cutaneous warts (41.6%, range 18-60 y)	• Injection of 0.3 mL measles-mumps-rubella (MMR) vaccine (30) • Topical wart paint containing salicylic acid and lactic acid in a collodion base (30)	Percent reduction in lesions, size of the largest lesion	There was a better therapeutic response with patients who received the MMR vaccine in comparison to the wart paint; in addition, patients with the wart paint showed relapse
Gaisin, 1976, US[18]	Case report	1 Out-patient (0%, 6 y)	• Lactic acid 15% and salicylic acid 15%	Adverse reactions	Lactic acid and salicylic acid generally serve well for treating warts in children; however, they should be used with caution, especially on the face
Khattar *et al.*, 2007, Lebanon[33]	Randomized, double-blind controlled trial	44 Out-patients Zinc oxide (44.5%, mean 25.8 y ± 8.1) Salicylic acid / Lactic acid (54.5%, mean 21.2 y ± 3.8)	• Zinc oxide (22) • Salicylic acid / Lactic acid (22)	Time to cure	Both interventions had a similar time to cure; zinc oxide may be promising to treat children due to simple and painless application
Niazi *et al.*, 2018, Pakistan[24]	Randomized controlled trial	210 Out-patients with common warts, not currently on medication Zinc oxide (11.9%, mean 26.89 y ± 12.461) Salicylic acid / Lactic acid (14.3%, mean 27.04 y ± 13.592)	• Zinc oxide 20% ointment (105) • Salicylic acid 15% / Lactic acid 15% (105)	Number and size of warts	The combination of salicylic acid and lactic acid is more effective than zinc oxide to treat common warts

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Shahmoradi *et al.*, 2015, Iran[40]	Randomized controlled trial	60 Out-patients with multiple plantar warts (36.7%, mean 30.2 y ± 12.3)	• Pyruvic acid (30) • Salicylic acid / Lactic acid (30)	Number and size of warts; complications and side effects; recurrence	Both treatments had similar effectiveness and safety in treating multiple plantar warts
Steele *et al.*, 1988, UK[26]	–	189 Out-patients with hand or plantar warts (gender and age not specified)	• Weekly liquid nitrogen (66) • Weekly liquid nitrogen plus daily wart paint (63) • Daily wart paint (60)	Wart cure	The combined treatment is significantly more effective than using either treatment separately for hand warts; however, no particular treatment showed success in the treatment of plantar warts
Sterling *et al.*, 2014, UK[47]	British Association of Dermatologists guideline	–	–	–	"The most commonly used, over-the-counter products are SA [salicylic acid] paints. These contain SA at concentrations of between 10% and 26% in either a collodion or a polyacrylic base; they are often mixed with lactic acid."
Indication 2: Melasma					
Abdel-Meguid *et al.*, 2017, Egypt[9]	Split face, right-left, assessor-blinded, randomized controlled study	24 Patients with melasma (0%, mean 34.5 y ± 7.76)	• Chemical peeling with trichloroacetic acid alone (24) • Chemical peeling with trichloroacetic acid plus Jessner's solution (24)	Melasma Area and Severity Index (MASI score)	The side treated with the combined Jessner's solution and trichloroacetic acid had a significantly greater decrease in MASI score compared to the side treated with just trichloroacetic acid

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Azzam *et al.*, 2009, Egypt[11]	Prospective, randomized study	45 Patients with epidermal or mixed melasma (0%, mean 34.16 y ± 6.76)	• Chemical peeling with Jessner's solution (15) • Chemical peeling with trichloroacetic acid 20% (15) • Topical hydroquinone 2% and kojic acid 2% (15)	MASI score	Trichloroacetic acid peeling may give better long-term improvement in melasma, though Jessner's solution seems to give more impressive and safer short-term improvement
Dayal, 2014, India[15]	–	40 Patients (gender not specified, range 21-40 y)	• Chemical peel of lactic acid 92% (20) • Chemical peel of lactic acid 92% plus topical regimen with hydroquinone 2%, tretinoin 0.025%, and mometasone furoate 0.1% (20)	MASI score	The topical regimen enhances the effectiveness of the lactic acid peel; it is safe, well-tolerated, and highly effective
Ejaz *et al.*, 2008, Pakistan[36]	Double-blind, randomized, interventional comparative study	60 Out-patients with melasma Jessner's solution (14%, mean 28.1 y) Salicylic acid (7.6%, mean 32.4 y)	• Jessner's solution (34) • Salicylic acid 30% (24)	MASI score	There was no significant difference in effectiveness and safety between the 2 interventions
Lawrence *et al.*, 1997, US[38]	Controlled clinical trial	16 Patients with melasma ranging from mild and discontinuous to severe and homogenous (0%, age not specified)	• Right side of face: glycolic acid 70% (16) • Left side of face: Jessner's solution (16)	Pigment changes (measured by colorimeter), MASI score	Both interventions work equally as well in the treatment of melasma, combined with tretinoin and hydroquinone between peels

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Lee *et al.*, 2014, Korea[39]	Single-center, randomized, controlled, double-blinded study	52 Patients with melasma Placebo (0%, mean 42.08y ± 6.92) Jessner's (0%, mean 40.85 y ± 7.48)	1064-nm QSNYL (Q-switched Nd:YAG laser) plus: • Placebo chemical peel (26) • Jessner's solution chemical peel (26)	Improvement in melasma severity; adverse events	"Both treatments were effective after 10 sessions of treatment but the final difference between the two groups were not significant…From this data, we can postulate that Jessner's solution had an early additive effect to laser treatment, but this effect was not consistent after four sessions of treatment."
Indication 3: Acne					
Bae *et al.*, 2013, Korea[29]	Split-face study	13 Patients with mild to moderate acne (100%, range 20-28y)	• Chemical peel with Jessner's solution (13) • Chemical peel with salicylic acid (13)	Inflammatory and non-inflammatory lesion count	Salicylic acid had comparable efficacy to Jessner's solution regarding inflammatory acne lesions, but showed better efficacy in non-inflammatory acne lesions
Colvan *et al.*, 2015, US[14]	Open-label, single center pilot study	8 Patients with moderate facial acne (gender not specified, range 23-37y)	• Chemical peel with lactic acid, salicylic acid, resorcinol, and retinol, in addition to twice daily application of novel acne cream (8)	Acne severity, acne lesion count	Combining the new acne lotion with a series of chemical peels may be a well-tolerated treatment for adult patients with moderate facial acne, in addition to post inflammatory hyperpigmentation or erythema
Dayal *et al.*, 2017, India[30]	Prospective, randomized, interindividual clinical trial	40 Patients with mild to moderate facial acne Salicylic acid peel (60%, mean 17.8 y ± 1.88) Jessner's solution peel (70%, mean 16.8 y ± 2.09)	• Chemical peel with salicylic acid 30% (20) • Chemical peel with Jessner's solution (20)	Michaelsson acne scores	While both salicylic acid peels and Jessner's solution peels are safe and well-tolerated, salicylic acid peels are more efficacious to treat mild to moderate facial acne in Indian patients

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Draelos *et al.*, 2016, US[16]	Clinical trial	27 Patients with mild to moderate acne (gender and age not specified)	• A 3-product regimen consisting of a: twice daily cleanser, twice daily acne serum, and a broad- spectrum SPF 50+ sunscreen as needed	Total inflammatory and non-inflammatory lesions	After 4 weeks, there was a statistically significant reduction in both inflammatory and non-inflammatory lesions, which continued into 8 weeks
In Jae *et al.*, 2018, Korea[32]	Prospective, randomized, evaluator-blind, split-face clinical trial	20 Out-patients who have had acne vulgaris for a mean of 8.9 y (40%, range 21-38 y)	• Chemical peel with glycolic acid 50% and salicylic acid 5% (20) • Jessner's solution (20)	Acne severity and lesion count (inflammatory, non-inflammatory, and total)	The glycolic acid chemical peel can be as effective and convenient as conventional peeling with Jessner's solution, and may have fewer adverse effects
Indication 4: Ichthyoses					
Ganemo *et al.*, 1999, Sweden[19]	Double-blind, within patient study	20 Patients with lamellar ichthyosis (gender and age not specified)	• Urea 5% in Locobase ® fatty cream (20) • Propylene glycol 20% in Locobase® fatty cream (20) • Lactic acid 5% and propylene glycol 20% in Locobase® fatty cream (20) • Lactic acid 5% and propylene glycol 20% in Essex® cream (20)	Scaling, dryness, and erythema scoring; skin capacitance; transepidermal water loss	Patients preferred the combination of lactic acid and propylene glycol in both cream bases; both formulations reduced hyperkeratosis and xerosis, though may still cause irritation and adversely affect the epidermal barrier function
Long, 2014, US[23]	Case report	1 Patient with ichthyosis with confetti (0%, 11 y)	• Lactic acid 10% with urea 20% in an Aquaphor compound	Management of skin cracking	Since there is no cure, the goal of treatment is to control symptoms with emollients

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Oji *et al.*, 2017, Germany[25]	German Society of Dermatology guideline	–	–	–	Lactic acid is a moisturizer and is well tolerated at low concentrations; it reduces keratoses
Indication 5: Photodamage					
Berson *et al.*, 2016, US[12]	Single-center clinical study	37 Patients with mild-to-moderate skin photodamage (0%, range 35-55 y)	• Chemical peel with salicylic acid / lactic acid / phenylethyl resorcinol (37)	Skin appearance (such as wrinkles and brightness)	Statistically significant improvements were observed when compared to baseline
Katz *et al.*, 2015, US[21]	Full-face clinical study	25 Out-patients with moderate-to-severe lines or wrinkles, grade 3 or higher on the Glogau Scale (0%, mean 54.1 y ± 8.9)	• Cream skin cleanser (l-lactic acid 7.8% / salicylic acid 2%), anti-aging serum (l-lactic acid 6.5% / Alpha hydroxy acid retinoid conjugate 0.1%), and sunscreen SPF 50+ (25)	Change between photodamage grade at the week 4 and 8 visits in comparison to the baseline visit	All of the study products were well-tolerated; investigators came to the conclusion that the alpha hydroxy acid retinoid conjugate is safe and effective and warrants further study
Tse *et al.*, 1996, US[34]	–	13 Patients with photodamaged facial skin (100%, age not specified)	• Right side: glycolic acid 70% followed by trichloroacetic acid 35% (13) • Left side: Jessner's solution followed by trichloroacetic acid 35% (13)	Clearing of actinic keratoses; lightening of solar lentigines and lessening of rhytides; histologic changes via biopsy	Neither intervention produced a dramatic improvement in rhytides

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 6: Actinic keratoses					
Lawrence *et al.*, 1995, US[22]	–	15 Out-patients with facial actinic keratoses (100%, age not specified)	• Jessner's peel followed by trichloroacetic acid (35%) on left side of the face (15) • Fluorouracil cream (5%) on right side of face twice daily for 3 weeks (15)	Number of visible actinic keratoses	Jessner's solution and trichloroacetic acid is effective to treat widespread facial actinic keratoses
Witheiler *et al.*, 1997, US[42]	Long term follow-up	15 Out-patients with facial actinic keratoses (100%, age not specified)	• Jessner's peel followed by trichloroacetic acid (35%) on left side of the face (15) • Fluorouracil cream (5%) on right side of face twice daily for 3 weeks (15)	Number of visible actinic keratoses	At the 32-month follow-up, the efficacy between the 2 interventions is similar, with no statistical difference between treatment groups
Indication 7: Active acne, epidermal melasma					
Khunger *et al.*, 2008, India[45]	Indian Association of Dermatologists guideline	–	–	–	Peels that are superficial or medium depth are safer for Indian patients
Indication 8: Aging neck skin					
Fulton *et al.*, 1999, US[17]	–	12 Patients receiving a neck skin rejuvenation program (gender and age not specified)	• Jessner-trichloroacetic acid peel (12)	A safe and effective method to rejuvenate the neck	The patients were pleased with the results of the program, though a minor loss of pigmentation was documented

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 9: Atrophic acne scarring					
Ali *et al.*, 2019, Egypt[10]	Comparative randomized clinical trial	60 Out-patients with atrophic acne scarring (gender and age not specified)	• Microneedling (20) • Chemical peeling with Jessner's solution (20) • Microneedling plus Jessner's solution (20)	Atrophic scarring	While all patients saw clinical improvement, regardless of intervention, significantly better results were achieved by a combination of Jessner's solution and microneedling than either alone
Indication 10: Chemical peels in skin types III-VI					
Vemula *et al.*, 2018, US[41]	Single center retrospective analysis	437 Peels on 132 patients with skin type III or higher (gender not specified, mean 40.3 y ± 10.9)	• Combination (177) • Glycolic acid • Lactic acid • Mandelic acid • Salicylic acid • Trichloroacetic acid	Short-term and long-term side effects	Superficial chemical peels have a relatively low complication rate in standardized administration on darker skin types
Indication 11: Facial hyperpigmentation					
Cohen *et al.*, 2012, US[13]	Case studies	8 In-patients with facial hyperpigmentation (12.5%, range 25-63 y)	• Chemical peel with resorcinol, lactic acid, salicylic acid, and retinoic acid followed by a 12-week topical regimen	Hyperpigmentation	The combination of 1 in-office procedure followed by a maintenance regimen at home can be an effective and well-tolerated treatment for hyperpigmentation

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 12: Frictional asymptomatic darkening of extensor surfaces					
Krishnamurthy *et al.*, 2005, US[44]	Case reports	9 Patients presenting with skin discoloration (33%, range 32-68 y)	• Lactic acid 12% (5) • Lactic acid 12% with OTC cream (1) • Urea 40% cream (1) • Urea 40% cream with vitamin E lotion (1) • Urea 40% cream with clobetasol cream and OTC moisturizers (1)	Improvement in skin discoloration	In most scenarios, treatment with either lactic acid or urea cream over 3-6 months is at least partially effective for treatment of frictional asymptomatic darkening of extensor surfaces
Indication 13: Gram-negative bacilli infection					
Hoffman *et al.*, 1978, US[20]	Case report	1 Outpatient (100%, 56 y)	• Oral co-trimoxazole and topical lactic acid 10% in hydrophilic emulsion base	Clearance of infection	This treatment led to the compete clearance of lesions over the next 3 months, with the exception of residual post-inflammatory changes in pigment
Indication 14: Keratosis pilaris					
Kootiratrakarn *et al.*, 2015, Thailand[37]	Prospective, randomized, and clinical study	50 Out-patients with keratosis pilaris (gender and age not specified)	• Lactic acid 10% • Salicylic acid 5%	Disease severity and percent improvement; high-frequency conductance; transepidermal water loss	Both lactic acid and salicylic acid can treat keratosis pilaris; there was significant clearance and marked improvement

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 15: Lichen planus pigmentosus					
Wolff *et al.*, 2016, US[27]	Case report	1 Out-patient with lichen planus pigmentosus (100%, 18 y)	• Topical azelaic acid 5% foam, tretinoin 0.1% cream, and chemical peels with Jessner's peel for his arms and glycolic acid peels for his face (1)	Change in dyspigmentation	While the dyschromia in the patient's arm lesions improved, there was less of a clinically dramatic change in the response on his face
Indication 16: Molluscum contagiosum					
Kibar Ozturk, 2019, Sudan[43]	Prospective, randomized, and comparative study	101 Patients with molluscum contagiosum (gender not specified, range 2-16 y)	• Potassium hydroxide 10% (54) • Salicylic acid 16.7% and lactic acid (47)	Complete or partial remission, side effects	Both interventions were shown to be effective in the treatment of molluscum contagiosum; neither was superior in treatment, though the salicylic acid and lactic acid combination had fewer side effects
Indication 17: Palmar-plantar erythrodysesthesia					
Wolf *et al.*, 2010, US[35]	2-arm, phase III, randomized clinical trial	137 Patients with palmar-plantar erythrodysesthesia who were scheduled to receive capecitabine for 14 days with at least 4 cycles planned at 21-day intervals Urea / Lactic acid (22%, age not specified) Placebo (18%, age not specified)	• Urea / Lactic acid (67) • Placebo (60)	Self-reported incidence of moderate-to-severe symptoms of palmar-plantar erythrodysesthesia (aka hand-foot syndrome)	The study does not support efficacy of the urea and lactic acid cream to prevent palmar-plantar erythrodysethesia in patients receiving capecitabine

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 18: Psoriasis					
Menter *et al.*, 2009, US[46]	American Academy of Dermatology guideline	Patients with mild or moderate disease or patients with more extensive disease who are receiving concurrent treatment with either ultraviolet light or systemic medications	–	–	It is not recommended to use topical agents as monotherapy in extensive disease or limited, but recalcitrant disease
Indication 19: Xerosis of the foot					
Grossman, 2011, US[28]	Single-center, open-label	12 Patients with xerosis of the foot (50%, range 41-70 y); 50% of the patients had diabetes	• Urea 35% in water-lipid-based foam delivery system with lactic acid	Safety and efficacy	"Significant improvement in the severity of xerosis was noted by the investigator in all of the participants who completed the study. Similarly, significant improvement... was observed...by the investigator and the participants for redness, scaling, and cracking."

Abbreviations: "–", not mentioned; MASI, Melasma Area and Severity Index; SA, salicylic acid.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Photodamage[12,21,34]	Apply once	–	Solution	Topical	Once
	–	6.5-7.8%	Cream, serum		8 weeks
	Apply every 4 weeks	–	–		16 weeks
Acne[14,16]	Apply every 4 weeks	–	–	Topical	12 weeks
	Apply twice daily	10.4%	Serum	Topical	8 weeks
Actinic keratoses[22,42]	Apply once	–	Solution	Topical	Once
		14%			
Aging neck skin[17]	Apply 3-4 coats	14%	Solution	Topical	Once
Chemical peels in skin types III-VI[41]	Repeat at least 2 weeks after initial peel	88%	–	Topical	At least once
Facial hyperpigmentation[13]	Apply once	–	Peel	Topical	Once
Frictional asymptomatic darkening of the extensor surfaces[44]	Apply twice daily	12%	Cream	Topical	1 month – 3 years
Ichthyosis with confetti[23]	Apply daily	–	Shampoo	Topical	Indefinite
	Apply thrice daily	10%	Lotion		
Infection caused by gram-negative bacilli[20]	–	10%	–	Topical	–
Lichen planus pigmentosus[27]	Apply every 2-4 weeks	–	Solution	Topical	16 weeks

Melasma[38]	Apply monthly with 2-3 coats	–	Solution	Topical	3 months
Palmar-plantar erythrodyesthesia[35]	Apply 0.5-1 teaspoon twice daily	6%	Cream	Topical	3 weeks
Psoriasis[46]	–	–	–	Topical	3 weeks
Warts[18]	Apply twice daily	15%	Flexible collodion	Topical	3 weeks
Xerosis of the foot[28]	Apply twice daily	–	Foam	Topical	4 weeks

Abbreviations: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Melasma[9,11,15,36,39,45]	Apply every 1-4 weeks	–	Solution	Topical	6-20 weeks
		14%			12 weeks
	Apply every 3 weeks	92%	Peel	Topical	18 weeks
Warts[24,26,31,33,40,47]	Apply twice daily	15%	–	Topical	3 months
	Apply daily	17%	Paint		–
	Apply twice weekly	16.7%			2 months
	Apply twice daily	15-16.7%	Ointment, solution		4 weeks – 3 months
Acne[29,30,32,45]	Apply 1-3 coats every 1-2 weeks	14%	Solution	Topical	6-12 weeks
					Twice
Ichthyoses[25], lamellar ichthyosis[19]	–	5%	Cream	Topical	–
	Apply twice daily				4 weeks
Atrophic acne scarring[10]	Apply every 2 weeks	85%	Solution	Topical	6-18 weeks
Keratosis pilaris[50]	Apply twice daily	10%	Cream	Topical	12 weeks
Molluscum contagiosum[43]	–	16.7%	Solution	Topical	Until lesions clear, maximum 30 days

Abbreviations: "–", not mentioned.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Lactic acid 5% / Ascorbyl palmitate 1% / Hyaluronic acid sodium salt 0.5% / Kojic acid 4% / Lactic acid 5% / Potassium azeloyl diglycinate 10% / Tretinoin	0
	Lactic acid 10% / Aloe Vera 0.2% / Fluocinolone acetonide 0.05% / Hyaluronic acid sodium salt 0.5% / Urea 10%	0
	Lactic acid 10% / Ascorbyl palmitate 1% / Hydrocortisone 0.5% / Kojic acid 4% / Potassium azeloyl diglycinate 10%	0
	Lactic acid 10% / Ascorbyl palmitate 1% / Kojic acid 4% / Niacinamide 4% / Potassium azeloyl diglycinate 10%	0
	Lactic acid 10% / Aloe Vera 1% / Urea 40%	0
	Lactic acid / Resorcinol / Salicylic acid • Lactic acid 14% / Resorcinol 14% / Salicylic acid 14% – Jessner's solution[9-11,17,22,29,30,32,36,39,42,45]	12
	Lactic acid 30% / Salicylic acid 30% • Lactic acid 15-17% / Salicylic acid 10-25% – flexible collodion paint;[18,26,31,40] not mentioned;[24,47] solution[43] • L-lactic acid 7.8% / Salicylic acid 2% – cream skin cleanser[21]	8
Others found in literature	Lactic acid / Resorcinol / Retinol / Salicylic acid – not mentioned[14]	1
	Lactic acid / Resorcinol / Retinoic acid / Salicylic acid – chemical peel[13]	1
	Lactic acid 10.4% / AHA retinoid conjugate 0.1% / Salicylic acid 2% – serum[16]	1
	Lactic acid / Phenylethyl rescorinol / Salicylic acid – not mentioned[12]	1
	L-lactic acid 6.5% / AHA retinoid conjugate 0.1% – anti-aging serum[21]	1
	Lactic acid 5% / Propylene glycol 20% – cream[19]	1
	Lactic acid 6-10% / Urea 12-35% – Aquaphor lotion;[23] cream;[35] foam[28]	3

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Actinic keratoses[22,42]	1995, 1997	• Resorcinol (14 g), lactic acid (14 g), and salicylic acid (14 g) were dissolved in ethanol to make a final solution	Solution	14%
Ichthyosis with confetti[23]	2014	• Mixture of lactic acid (10%) and urea (20%) with Aquaphor	Lotion	10%

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Melasma[36,39]	• Jessner's solution composed of lactic acid (14%), resorcinol (14%), and salicylic acid (14%) was "prepared in the institute's pharmacy on weight-to-volume basis in hydroethanolic solution"	Solution	14%
	• Jessner's solution was prepared with lactic acid (14 g), resorcinol (14 g), and salicylic acid (14 g) dissolved in 95% ethanol	Solution	14%

Summary of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, 189 declined or failed to respond to the interview request. One SME discussed lactic acid. The SME was a medical doctor who was board-certified in dermatology, working as a consultant, formerly in an academic medical center. The SME had been in practice for 40 years.

The SME commented that the lower concentrations of lactic acid, such as those seen in many OTC products, are typically used for dry skin as an exfoliant, like urea and salicylic acid. As one of the many AHAs, lactic acid makes the skin appear smoother by taking off the top layer of skin. As a keratolytic, lactic acid can be used on ichythyosis, the most common of which is ichthyosis vulgaris. Ichythosis vulgaris is particularly common in the Northeast during the winter, amongst the Irish Celtic population, and presents as little fish-like scales on their anterior shins. Some other indications for which the use of lactic acid is well-established include debulking a plantar wart, taking a toenail off that has a fungal infection, or doing superficial peels in an office for someone with melasma. These uses are unlikely to cause a significant safety issue, and the SME did not see a high risk to the use of lactic acid for these conditions.

The SME was not aware of a scenario where they would use lactic acid up to 88%, since this is typically used in cosmetic procedures and the practitioner "would probably fry the first few cell layers if you put that on the skin."

When asked about the use of lactic acid in combination, the SME said that kojic acid is used for patients with melasma, while hydrocortisone or fluocinonide are used to help stop inflammation. Another active ingredient, niacinamide, is used to provide B vitamins to the skin, and will also help to raise the acid pH, to keep it from being too low. Niacinamide is also used to help patients rebuild collagen and elastin after superficial laser procedures.

Results of survey

Six people responded to the survey; refer to Table 11 for respondent characteristics.

Among respondents, 5 (83%) used lactic acid and 1 (17%) did not use lactic acid. Of the respondents who reported using lactic acid, 5 (100%) said that they use lactic acid as a topical dosage form (e.g. cream, gel, ointment). Regarding nominated indications, 1 (20%) used lactic acid for seborrheic dermatitis, 2 (40%) for warts, and 0 (0%) for periorbital melanosis (refer to Table 12). Four (80%) respondents also reported using lactic acid for indications that were not nominated. These indications were chemical peels, comedonal acne and keratosis pilaris, melasma and xerosis, and "not available as standalone Rx for topical [use]".

For the 5 respondents who reported using lactic acid, reasons for utilizing the compounded product included: lack of commercial products in an appropriate dosage form, strength, or combination (2, 40%), patient allergies (2, 40%), other patient conditions preventing use of commercial products (2, 40%), or no commercially available products with lactic acid (1, 20%). Two (40%) respondents said that they used compounded lactic acid for reasons not listed, though only 1 provided an explanation. One (20%) respondent provided further explanation; "Jessner's Solution is 14% strength…way too strong," and "a good alternative to topical retinoids for acne and have found it to be much more effective for KP (keratosis pilaris) than commercially available products." Refer to Table 13 for reasons for using compounded lactic acid.

All of the respondents (5, 100%) who said that they use lactic acid reported stocking non-patient-specific compounded lactic acid at their practice. These respondents purchased, or had the patient purchase, the

product from a compounding pharmacy (2, 40%) or outsourcing facility (3, 60%). Refer to Table 14 for how respondents obtained compounded lactic acid.

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	**Responses, n (N=6)**
Doctor of Medicine (MD)	3
Doctor of Osteopathic Medicine (DO)	1
Nurse Practitioner (NP)	1
No Response	1
Practice Setting	**Responses, n (N=6)**
Physician office or private practice	5
No response	1

Table 12. Conditions for which lactic acid prescribed or administered

Condition	**Responses, n (N=5)[a,b]**
Seborrheic dermatitis	1
Warts	2
Periorbital melanosis	0
Other[c]	4

[a]Out of 6 respondents, 5 reported prescribing or using lactic acid.
[b]Some respondents reported more than one condition for using lactic acid.
[c]Chemical peels, comedonal acne and keratosis pilaris, melasma and xerosis, and "not available as standalone Rx for topical [use]" were not nominated.

Table 13. Reasons for using compounded lactic acid

Reason	Responses, n (N=5)[a,b]
Commercial product not available in desired dosage form, strength or combination	2
Patient allergies prevent use of commercial products	2
Patient conditions prevent use of commercial products	2
No commercial products	1
Other – Lactic Acid is not available as a 505-approved drug as a standalone drug product intended for topical application	1

[a]Out of 6 respondents, 5 reported prescribing or using lactic acid.
[b]Some respondents reported more than one reason for using compounded lactic acid.

Table 14. Use of non-patient-specific compounded lactic acid

Do you stock non-patient-specific compounded lactic acid at your practice?	**Responses, n (N=5)[a]**
Yes	5
No	0
How do you obtain your stock of non-patient-specific compounded lactic acid?	
Compound yourself at practice	0
Product compounded by in-house pharmacy	0
Purchase, or have a patient purchase, from compounding pharmacy	2
Purchase, or have a patient purchase, from outsourcing facility	3

[a]Out of 6 respondents, 5 reported prescribing or using lactic acid.

CONCLUSION

Lactic acid was nominated for inclusion on the 503B Bulks List for topical use in various dosage forms, including gel, cream, solution, shampoo, etc., to treat unknown medical conditions, although it is generally used to treat seborrheic dermatitis, warts, and periorbital melanosis. Topical lactic acid products are approved for use in Abu Dhabi, Australia, Ireland, Namibia, Saudi Arabia, and the UK. It is also available as an OTC product in the US.

From the literature review and interviews conducted, lactic acid was used in concentrations ranging from 6-92%, both as single-ingredient products and in combination with a variety of APIs. The SME considered the use of lactic acid well-established and safe for indications such as debulking a plantar wart, taking off a toenail with a fungal infection, or doing superficial peels for melasma. However, the SME was not aware of a scenario where they would use lactic acid at a concentration as high as 88%, although the SME stated this may be done as part of a cosmetic procedure. The SME noted that kojic acid is used for patients with melasma, the addition of hydrocortisone or fluocinonide to combination products is to help stop inflammation, and niacinamide is used to help raise the acid pH and to help patients rebuild collage and elastin after superficial laser procedures. Through the literature review, salicylic acid was the API that was most often used with lactic acid.

From the survey responses, 5 out of 6 respondents used lactic acid. The most common indication respondents used compounded lactic acid for was warts. Lack of appropriate commercial product, patient allergies, other patient conditions preventing use of commercial product, and no available commercial products with lactic acid were some of the reasons for using the compounded lactic acid product over an FDA-approved product. Five respondents reported stocking non-patient specific compounded lactic acid at their practice.

REFERENCES

1. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology: Theory and Practice.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: Advancing the methodology. *Implementation Science.* 2010;5(1).
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143-143.
6. Dayal S, Sahu P, Jain VK, Khetri S. Clinical efficacy and safety of 20% glycolic peel, 15% lactic peel, and topical 20% vitamin C in constitutional type of periorbital melanosis: a comparative study. *Journal of cosmetic dermatology.* 2016;15(4):367-373.
7. Emtestam L, Svensson Å, Rensfeldt K. Treatment of seborrhoeic dermatitis of the scalp with a topical solution of urea, lactic acid, and propylene glycol (K301): results of two double-blind, randomised, placebo-controlled studies. *Mycoses.* 2012;55(5):393-403.
8. Smith WP. Epidermal and dermal effects of topical lactic acid. *Journal of the American Academy of Dermatology.* 1996;35(3 Pt 1):388-391.
9. Abdel-Meguid AM, Taha EA, Ismail SA. Combined Jessner solution and trichloroacetic acid Vversus trichloroacetic acid alone in the treatment of melasma in dark-skinned patients. *Dermatologic Surgery.* 2017;43(5):651-656.
10. Ali B, ElMahdy N, Elfar NN. Microneedling (Dermapen) and Jessner's solution peeling in treatment of atrophic acne scars: a comparative randomized clinical study. *Journal of Cosmetic and Laser Therapy.* 2019;21(6):357-363.
11. Azzam OA, Leheta TM, Nagui NA, Shaarawy E, Hay RM, Hilal RF. Different therapeutic modalities for treatment of melasma. *Journal of Cosmetic Dermatology.* 2009;8(4):275-281.
12. Berson D, Du A, Yatskayer M, Lynch S, Krol Y, Oresajo C. Clinical efficacy and tolerance of a chemical peel on women with mild to moderate photodamaged facial skin. *Journal of the American Academy of Dermatology.* 2016;74(5):AB25.
13. Cohen JL, Makino E, Sonti S, Mehta P. Synergistic combination of an in-office procedure and home regimen for the treatment of facial hyperpigmentation. *Journal of Clinical and Aesthetic Dermatology.* 2012;5(4):33-35.
14. Colvan L, Goberdhan L, Makino E, Mehta R. Pilot study: Efficacy and tolerability of a nondrying topical lotion combined with chemical peels in adult subjects with moderate facial acne and postinflammatory lesions. *Journal of the American Academy of Dermatology.* 2015;72(5):AB9.
15. Dayal S. Clinical evaluation of efficacy of lactic acid peeling in combination with a topical regimen in the treatment of melasma. *Pigment Cell and Melanoma Research.* 2014;27(5):966.
16. Draelos Z, Lewis J, McHugh L, Pellegrino A, Popescu L. Novel retinoid ester in combination with salicylic acid for the treatment of acne. *Journal of Cosmetic Dermatology.* 2016:36-42.

17. Fulton JE, Rahimi AD, Helton P, Dahlberg K. Neck rejuvenation by combining Jessner/TCA peel, dermasanding, and CO2 laser resurfacing. *Dermatologic Surgery.* 1999;25(10):745-750.

18. Gaisin A. Facial scarring due to topical wart treatment. *Archives of Dermatology.* 1976;112(12):1791-1792.

19. Ganemo A, Virtanen M, Vahlquist A. Improved topical treatment of lamellar ichthyosis: a double-blind study of four different cream formulations. *British Journal of Dermatology.* 1999;141(6):1027-1032.

20. Hoffman TE, Russell B, Jacobs PH. Mycetoma-like infection caused by previously undescribed bacterium. *Archives of Dermatology.* 1978;114(8):1199-1202.

21. Katz BE, Lewis J, McHugh L, Pellegrino A, Popescu L. The tolerability and efficacy of a three-product anti-aging treatment regimen in subjects with moderate-to-severe photodamage. *The Journal of Clinical & Aesthetic Dermatology.* 2015;8(10):21-26.

22. Lawrence N, Cox SE, Cockerell CJ, Freeman RG, Cruz Jr PD. A comparison of the efficacy and safety of Jessner's solution and 35% trichloroacetic acid vs 5% fluorouracil in the treatment of widespread facial actinic keratoses. *Archives of Dermatology.* 1995;131(2):176-181.

23. Long MC. Ichthyosis with confetti: A rare diagnosis and treatment plan. *BMJ Case Reports.* 2014.

24. Niazi BR, Farid Ur R. Efficacy of 20% zinc oxide paste versus 15% salicylic acid - 15% lactic acid combination in treatment of common viral warts. *Journal of Pakistan Association of Dermatologists.* 2018;28(3):333-336.

25. Oji V, Preil ML, Kleinow B, et al. S1 guidelines for the diagnosis and treatment of ichthyoses – update. *JDDG - Journal of the German Society of Dermatology.* 2017;15(10):1053-1065.

26. Steele K, Irwin WG. Liquid nitrogen and salicylic/lactic acid paint in the treatment of cutaneous warts in general practice. *Journal of the Royal College of General Practitioners.* 1988;38(311):256-258.

27. Wolff M, Sabzevari N, Gropper C, Hoffman C. A case of lichen planus pigmentosus with facial dyspigmentation responsive to combination therapy with chemical peels and topical retinoids. *The Journal of Clinical & Aesthetic Dermatology.* 2016;9(11):44-50.

28. Grossman AB. Clinical evaluation of 35% urea in a water-lipid-based foam containing lactic acid for treatment of mild-to-moderate xerosis of the foot. *Journal of the American Podiatric Medical Association.* 2011;101(2):153-158.

29. Bae BG, Park CO, Shin H, et al. Salicylic acid peels versus Jessner's solution for acne vulgaris: A comparative study. *Dermatologic Surgery.* 2013;39(1):248-252.

30. Dayal S, Amrani A, Sahu P, Jain VK. Jessner's solution vs. 30% salicylic acid peels: a comparative study of the efficacy and safety in mild-to-moderate acne vulgaris. *Journal of Cosmetic Dermatology.* 2017;16(1):43-51.

31. Deshmukh AR, Nawale SS, Patil SS, Pawar SS. The efficacy of measles-mumps-rubella vaccine versus salicylic acid-lactic paint in the treatment of warts. *Indian Journal of Dermatology, Venereology & Leprology.* 2020;05:05.

32. In Jae J, Dong Ju H, Dong Hyun K, Yoon MS, Lee HJ. Comparative study of buffered 50% glycolic acid (pH 3.0) + 0.5% salicylic acid solution vs Jessner's solution in patients with acne vulgaris. *Journal of Cosmetic Dermatology.* 2018;17(5):797-801.

33. Khattar JA, Musharrafieh UM, Tamim H, Hamadeh GN. Topical zinc oxide vs. salicylic acid-lactic acid combination in the treatment of warts. *International Journal of Dermatology.* 2007;46(4):427-430.

34. Tse Y, Ostad A, Lee HS, et al. A clinical and histologic evaluation of two medium-depth peels: Glycolic acid versus Jessner's trichloroacetic acid. *Dermatologic Surgery.* 1996;22(9):781-786.

35. Wolf SL, Qin R, Menon SP, et al. Placebo-controlled trial to determine the effectiveness of a urea/lactic acid-based topical keratolytic agent for prevention of capecitabine-induced hand-foot syndrome: North Central Cancer Treatment Group Study N05C5. *Journal of Clinical Oncology.* 2010;28(35):5182-5187.

36. Ejaz A, Raza N, Iftikhar N, Muzzafar F. Comparison of 30% salicylic acid with Jessner's solution for superficial chemical peeling in epidermal melasma. *Jcpsp, Journal of the College of Physicians & Surgeons - Pakistan.* 2008;18(4):205-208.

37. Kootiratrakarn T, Kampirapap K, Chunhasewee C. Epidermal permeability barrier in the treatment of keratosis pilaris. *Dermatology Research and Practice.* 2015;2015.

38. Lawrence N, Cox SE, Brody HJ. Treatment of melasma with Jessner's solution versus glycolic acid: a comparison of clinical efficacy and evaluation of the predictive ability of Wood's light examination. *Journal of the American Academy of Dermatology.* 1997;36(4):589-593.

39. Lee DB, Suh HS, Choi YS. A comparative study of low-fluence 1064-nm Q-switched Nd:YAG laser with or without chemical peeling using Jessner's solution in melasma patients. *Journal of Dermatological Treatment.* 2014;25(6):523-528.

40. Shahmoradi Z, Assaf F, Al Said H, Khosravani P, Hosseini SM. Topical pyruvic acid (70%) versus topical salicylic acid (16.7%) compound in treatment of plantar warts: A randomized controlled trial. *Advanced Biomedical Research.* 2015;4:113.

41. Vemula S, Maymone MBC, Secemsky EA, et al. Assessing the safety of superficial chemical peels in darker skin: A retrospective study. *Journal of the American Academy of Dermatology.* 2018;79(3):508-513.e502.

42. Witheiler DD, Lawrence N, Cox SE, Cruz C, Cockerell CJ, Freemen RG. Long-term efficacy and safety of Jessner's solution and 35% trichloroacetic acid vs 5% fluorouracil in the treatment of widespread facial actinic keratoses. *Dermatologic Surgery.* 1997;23(3):191-196.

43. Kibar Ozturk M. Efficacy and side effects of topical applications of two different solutions in the treatment of molluscum contagiosum in a city in africa: An open, randomized, comparative clinical trial. *Journal of Pediatric Infectious Diseases.* 2019;14(5):248-252.

44. Krishnamurthy S, Sigdel S, Brodell RT. Frictional asymptomatic darkening of the extensor surfaces. *Cutis.* 2005;75(6):349-355.

45. Khunger N, Force IT. Standard guidelines of care for chemical peels. *Indian Journal of Dermatology, Venereology & Leprology.* 2008;74 Suppl:S5-12.

46. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *Journal of the American Academy of Dermatology.* 2009;60(4):643-659.

47. Sterling JC, Gibbs S, Haque Hussain SS, Mohd Mustapa MF, Handfield-Jones SE. British Association of Dermatologists' guidelines for the management of cutaneous warts 2014. *British Journal of Dermatology.* 2014;171(4):696-712.

48. Huang CK, Miller TA. The truth about over-the-counter topical anti-aging products: A comprehensive review. *Aesthetic Surgery Journal.* 2007;27(4):402-412.

49. Soleymani T, Lanoue J, Rahman Z. A practical approach to chemical peels: A review of fundamentals and step-by-step algorithmic protocol for treatment. *Journal of Clinical and Aesthetic Dermatology*. 2018;11(8):21-28.

50. Kootiratrakarn T, Kampirapap K, Chunhasewee C. Epidermal permeability barrier in the treatment of keratosis pilaris. *Dermatology research & Practice.* 2015;2015:205012.

APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to April 10, 2020
- Date last searched: April 13, 2020
- Limits: Humans (search hedge); English language
- Number of results: 205

1	lactic acid/	42025
2	(lactic$ adj2 acid$).tw.	37009
3	milchsaure.tw.	1
4	milk acid$.tw.	125
5	jessner$.tw.	196
6	or/1-5	69335
7	administration, topical/	38134
8	administration, cutaneous/	21850
9	chemexfoliation/	744
10	topical$.tw.	103365
11	cutaneous$.tw.	149117
12	transcutaneous$.tw.	14192
13	transdermal$.tw.	14327
14	chem?exfoliat$.tw.	34
15	chem? exfoliat$.tw.	2
16	((chemical or skin) adj2 (exfoliat$ or peel$)).tw.	1432
17	emollients/	1821
18	pharmaceutical solutions/	3295
19	exp gels/	50920
20	suspensions/	7701

21	liniments/	123
22	ointments/	12748
23	skin cream/	986
24	emollient?.tw.	1721
25	gel?.tw.	304878
26	suspension?.tw.	107213
27	liniment?.tw.	143
28	ointment?.tw.	11693
29	salve?.tw.	339
30	paste?.tw.	12204
31	unguent$.tw.	113
32	lotion?.tw.	2268
33	cream?.tw.	18587
34	pomade?.tw.	89
35	cleanser?.tw.	1031
36	shampoo?.tw.	1379
37	face wash$.tw.	189
38	facial wash$.tw.	10
39	body wash$.tw.	251
40	paint?.tw.	8018
41	varnish$.tw.	3085
42	tonic?.tw.	31456
43	or/7-42	793720
44	drug therapy, combination/	164475
45	aloe/	1352
46	fluocinolone acetonide/	1362

47	hydrocortisone/	71455
48	hyaluronic acid/	21215
49	niacinamide/	12374
50	salicylic acid/	6443
51	tretinoin/	22025
52	urea/	43083
53	aloe?.tw.	2657
54	ghrita kumari.tw.	0
55	kanyasara.tw.	0
56	lu hui.tw.	3
57	luhui.tw.	7
58	(ascorb$ adj2 palmitat$).tw.	266
59	ascorbylpalmitat$.tw.	3
60	(flu?cino$ adj2 acetonid$).tw.	695
61	fluortriamcinolon$.tw.	0
62	h#drocorticosteroid$.tw.	16
63	h#dro#ortisat$.tw.	2
64	h#dro#ortison$.tw.	16225
65	h#dro#ortisyl.tw.	1
66	h#dro#orton$.tw.	15
67	hyaluron$.tw.	35477
68	(koji$ adj2 acid$).tw.	852
69	amide pp.tw.	2
70	nicotinamid$.tw.	20804
71	niacetamid$.tw.	0
72	niacinamid$.tw.	491

73	nicamid$.tw.	0
74	nicosedin$.tw.	0
75	nicotami#$.tw.	10
76	nicotinami#$.tw.	20821
77	(nicotinic adj2 amid$).tw.	92
78	nicotinoylami#$.tw.	13
79	nicotinsaureamid$.tw.	0
80	vitamin$ b3.tw.	383
81	vitamin$ pp.tw.	136
82	(potassium adj2 azeloyl).tw.	4
83	azeloglycin$.tw.	1
84	re#orc?in$.tw.	3176
85	recorcon$.tw.	0
86	salicylic acid$.tw.	12339
87	hydroxybenzoic acid$.tw.	2567
88	retinoic acid$.tw.	31764
89	trentin$.tw.	201
90	tretinoin$.tw.	1346
91	vitamin$ a acid$.tw.	354
92	vitamin$ a1 acid$.tw.	0
93	urea?.tw.	82592
94	or/44-93	467855
95	and/6,43,94	277
96	exp animals/ not humans/	4689514
97	95 not 96	222
98	limit 97 to english language	205

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 13, 2020
- Limits: Humans (search hedge); English language
- Number of results: 581

1	lactic acid'/de	81320
2	(lactic* NEAR/2 acid*):ti,ab,tn	48416
3	milchsaure':ti,ab,tn	6
4	milk acid*':ti,ab,tn	152
5	jessner*':ti,ab,tn	296
6	#1 OR #2 OR #3 OR #4 OR #5	110778
7	topical drug administration'/de	81609
8	cutaneous drug administration'/de	624
9	transdermal drug administration'/de	8887
10	chemexfoliation'/de	431
11	topical*':ti,ab	146634
12	cutaneous*':ti,ab	213984
13	transcutaneous*':ti,ab	18994
14	transdermal*':ti,ab	20873
15	chem$exfoliat*':ti,ab	36
16	chem$ exfoliat*':ti,ab	3
17	((chemical OR skin) NEAR/2 (exfoliat* OR peel*)):ti,ab	1936
18	emollient agent'/de	5856
19	drug solution'/de	3041
20	gel'/exp	73875
21	liniment'/de	248
22	lotion'/de	2810

23	ointment'/exp	18395
24	paste'/de	2491
25	pomade'/de	81
26	salve'/de	165
27	suspension'/exp	108971
28	shampoo'/de	2256
29	cream$':ti,ab	29083
30	liniment$':ti,ab	231
31	lotion$':ti,ab	3945
32	ointment$':ti,ab	21317
33	paste$':ti,ab	14679
34	pomade$':ti,ab	141
35	salve$':ti,ab	471
36	varnish*':ti,ab	3361
37	unguent*':ti,ab	239
38	shampoo*':ti,ab	2322
39	body wash*':ti,ab	377
40	face wash*':ti,ab	256
41	facial wash*':ti,ab	19
42	cleanser*':ti,ab	1521
43	paint$':ti,ab	10542
44	tonic$':ti,ab	45441
45	suspension$':ti,ab	142720
46	gel$':ti,ab	357974
47	emollient$':ti,ab	3063
48	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	1140537

	OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47	
49	combination drug therapy'/de	11074
50	aloe vera'/de	2158
51	ascorbyl palmitate'/de	383
52	fluocinolone acetonide'/de	3203
53	hydrocortisone'/de	139993
54	hyaluronic acid'/de	42863
55	kojic acid'/de	1600
56	nicotinamide'/de	15725
57	resorcinol'/de	3716
58	salicylic acid'/de	25967
59	retinoic acid'/de	41853
60	urea'/de	82716
61	aloe$':ti,ab,tn	4207
62	ghrita kumari':ti,ab,tn	1
63	kanyasara':ti,ab,tn	1
64	lu hui':ti,ab,tn	2
65	luhui':ti,ab,tn	6
66	(ascorb* NEAR/2 palmitat*):ti,ab,tn	336
67	ascorbylpalmitat*':ti,ab,tn	7
68	(flu$cino* NEAR/2 acetonid*):ti,ab,tn	1072
69	fluortriamcinolon*':ti,ab,tn	0
70	hydrocorticosteroid*':ti,ab,tn	56
71	hydrocortisat*':ti,ab,tn	10
72	hydrocortison*':ti,ab,tn	27262
73	hydrocortisyl':ti,ab,tn	15

74	hydrocorton*':ti,ab,tn	162
75	hidrocorticosteroid*':ti,ab,tn	0
76	hidrocortisat*':ti,ab,tn	0
77	hidrocortison*':ti,ab,tn	22
78	hidrocortisyl':ti,ab,tn	0
79	hidrocorton*':ti,ab,tn	0
80	hydrokortison*':ti,ab,tn	7
81	hyaluron*':ti,ab,tn	48600
82	(koji* NEAR/2 acid*):ti,ab,tn	1114
83	nicotinamid*':ti,ab,tn	25260
84	niacetamid*':ti,ab,tn	0
85	niacinamid*':ti,ab,tn	776
86	nicamid*':ti,ab,tn	1
87	nicosedin*':ti,ab,tn	0
88	nicotamid*':ti,ab,tn	26
89	nicotamin*':ti,ab,tn	0
90	nicotinamin*':ti,ab,tn	21
91	nicotinamid*':ti,ab,tn	25260
92	(nicotinic NEAR/2 acid*):ti,ab,tn	9532
93	nicotinoylamin*':ti,ab,tn	18
94	nicotinoylamid*':ti,ab,tn	2
95	nicotinsaureamid*':ti,ab,tn	6
96	nikotamin*':ti,ab,tn	0
97	vitamin* b3':ti,ab,tn	463
98	vitamin* pp':ti,ab,tn	295
99	amide pp':ti,ab,tn	2

100	(potassium NEAR/2 azeloyl):ti,ab,tn	5
101	azeloglycin*':ti,ab,tn	2
102	resorc$in*':ti,ab,tn	4317
103	recorcin*':ti,ab,tn	3
104	recorcon*':ti,ab,tn	0
105	salicylic acid*':ti,ab,tn	14838
106	hydroxybenzoic acid*':ti,ab,tn	3233
107	retinoic acid*':ti,ab,tn	38160
108	trentin*':ti,ab,tn	269
109	tretinoin*':ti,ab,tn	2051
110	vitamin* a acid':ti,ab,tn	466
111	vitamin* a1 acid':ti,ab,tn	0
112	urea$':ti,ab,tn	112649
113	#49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112	494956
114	#6 AND #48 AND #113	736
115	[animals]/lim NOT [humans]/lim	6015158
116	#114 NOT #115	650
117	#114 NOT #115 AND [english]/lim	581

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded lactic acid. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,
Dr. Ashlee Mattingly, Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer lactic acid to your patients?

    - o Yes
    - o No

3. Do you prescribe or administer lactic acid by any of the following dosage forms and/or routes of administration? (check all that apply)

    - o Topical dosage forms (e.g. cream, gel, ointment)
    - o None of the above

4. I prescribe or administer lactic acid for the following conditions or diseases: (check all that apply)

    - o Periorbital melanosis
    - o Seborrheic dermatitis
    - o Warts
    - o Other (please explain) _____

5. I use compounded lactic acid because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing lactic acid.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded lactic acid at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded lactic acid from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.